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Review

Helicobacter pylori infection and gastrointestinal hormones: a review

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INTRODUCTION

Helicobacter pylori (Hp) infection is closely related to gastrointestinal hormones and involves the formation of gastritis, gastric carcinoma and peptic ulcer[1-7]. Its pathogenesis relevant to pathophysiological changes of gastrointestinal hormones are described as follows according to individual hormone.

*H*P INFECTION AND GASTRIN

Gastrin is a basic stimulus to parietal cells in producing gastric acid, and shows two ways in acid production: one directly stimulates parietal cell and the other acts on enterochromaffin-like (ECL) cell to release histamine by which stimulates parietal cells. So the formation of gastric acid and hyperchlorhydria is one of the physiopathological implications of gastrin. *H*p infection in patients leading to increased release of gastrin from antral G cells and hyperga strinemia formation is currently an interesting medical problem[8-11].

Hypergastrinemia produced by Hp infection

It is well known that *H*p infection induces hypergastrinemia. In patients with normal gastroscopic features, those infected with *H*p had significantly higher basal serum gastrin levels than non-infected individuals, and were similar to DU patients who are almost entirely infected with *H*p. Therefore, hypergastrinemia seems to be associated with *H*p infection, and is not a distinctive feature of DU disease[12].

*H*p-infected hypergastrinemia may be produced by cytokines[13,14]: ① TNF-α: antral G cells (both human and canine) unde rgoing TNF-α- pretreatment significantly increased in both basal and bombesin-stimulated gastrin release (compared to control); TNF-α increased in *H*p infection,so the *H*p-infected hypergastrinemia may be due to TNF-α- stimulation to G cells; ② IL-8: IL-8 stimulated gastrin release from isolated G cells, and this effect was dose-dependent and potentiated by *H*p extract products.

The density of antral G cells was evaluated by expression of gastrin mRNA. The G cell density in patients with *H*p infection was significantly higher than in controls; after eradication of *H*p, the density was significantly lower as compared with pre-eradication value. The study suggests that increased gastrin mRNA is directly related to *H*p infection[15].

In a study of DU and non-ulcer dyspepsia (NUD), the *H*p (absence of CagA gene and presence of VacA alleles s2 and m2) was only found in NUD (not with DU), and associated with lesser extent of gastrin increase and higher value of tryptase. The CagA negative s2m2 strain of *H*p may be less dangerous for the gastric mucosa than other *H*p strains, since it enhances tryptase production by gastric mucosal mast cells. This enzyme is thought to stimulate tissue turnover and favour wound healing[16]. We may predict that the development of DU or NUD would probably depend upon the strains of *H*p.

Combined serum levels of gastrin and pepsinogen (PG) were used to study *H*p infection[17-19]. As a screening procedure to show the status of *H*p infection, both levels significantly increased in *H*p infection, and significantly decreased after *H*p eradication. The high levels may indicate *H*p infection and the significant decrease after treatment may indicate cure, and reappearance of high levels suggests reinfection. The level of PG-IIcould be more useful in this situation[18]. To classify DU, serum PG-I concentrations reflect the chief cell mass. Blood samples were taken before and at 15,30, and 60min after test meal, and the serum concentrations of fasting PG-I and gastrin were measured after meal. The area, under the serum gastrin 1h curve, was taken as integrated gastrin response (IGR). The DU patients (*H*p positive) were divided into two groups (hyper-IGR and normal-IGR, with significant difference). The hyper-IGR DU patients

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had higher serum PG-I concentrations, and suggest to be acid hypersecretors[19].

Change of acid (parietal cells) sensitivity to gastrin. In a study of three groups of subjects (DU patients, *H*p-negative and *H*p-positive healthy volunteers), the MAO (maximal acid output), and the acid sensitivity to gastrin were measured (serum gastrin required to achieve 50% MAO during intravenous administration of gastrin). The result revealed that the *H*p positive healthy volunteers showed significantly higher gastrin concentrations, which meant less sensitive than the other two groups. The DU group had significantly higher MAO. Conclusively, a combination of decreased sensitivity to gastrin in infected healthy volunteers and increased maximal acid secretory capacity in patients with DU underlies their different acid response to *H*p-induced hypergastrinemia, and they are caused by the hypergastrinemia[8].

In patients with end stage of renal disease on dialysis, the hypergastrinemia was induced by *H*p infection in stomach, and the serum gastrin concentrations were decreased to normal range following eradication of *H*p[20]. Either *H*p infection or omeprazole administration can cause hypergastrinemia, and both of them would cause severe hypergastrinemia, which may exert potential deleterious effects. Since omeprazole treatment produced a similar percentage increase in serum gastrin, it is appropriate to eradicate *H*p prior to commencing proton pump inhibitor treatment in order to reduce the degree of hypergastrinemia[21,22].

Evidence indicated that gastrin concentrations decreased to normal range after *H*p eradication[11,23-26].

*H*p INFECTION AND SOMATOSTATIN (SS)

Hp infection and D cells

*H*p infection is associated with exaggeration of gastrin release following meals or bombesin stimulation attributed to a defect of SS secretion of antral D cells[27,28]. Mucosal cytokines (TNF-α and IL-8 are predominant ones) were increased in *H*p infection. TNF-α- could stimulate the isolated canine gastric D cells to increase SS release dose-dependently, and the stimulatory effect was potentiated by IL-8 and inhibited by octreotide. In conclusions, TNF-α can regulate SS release from cultured D cells in a divergent manner[29].

SS inhibition on Hp proliferation

In *H*p infection, SS contents in antral mucosa and gastric juice, and number of D cells were decreased, and less expressions of SS mRNA and *H*p eradication resulted in restoration of those indices, suggesting the *H*p inhibition on SS release. In different SS concentrations *in vitro*, SS at 10^{-11}mol·L^{-1} significantly suppressed the proliferation of cultured *H*p. SS at a similar level in human gastric juice ($\approx 10^{-11}$mol·L^{-1}) indicated an inhibitory effect of SS in the gastric lumen on *H*p proliferation in humans[30].

Lipopolysaccharide (LPS) of Hp and SS

LPS inhibits the binding of SS to its gastric mucosal receptors. The antiulcer agents, sucralfate, ebrotidine and sulglycotide, possess the ability to restore the receptor-SS binding by 92.5%, 94.9% and 84%, respectively. Conclusively, LPS of *H*p inhibits the SS binding to its receptor, and results in less SS effect, more gastrin and gastric acid secretion, and ulcer formation[31,32].

Hp infection and gastrin-somatostatin equilibrium[33-41]

SS from D cells inhibits G cells, and decreased SS results in increase in gastrin secretion; gastrin stimulates, and SS inhibits parietal cells in gastric acid release. So, gastrin and SS form the gastrin-SS equilibrium, which was even called mechanism of gastric regulatory physiology. Phenomena related to imbalance of gastrin-SS equilibrium are as follows: ① hypergastrinemia: *H*p infection influences D cells firstly to diminish SS release, then increases release of gastrin and acid, leading to the milieu favoring ulcer formation; eradication of *H*p gets rid of the imbalance; the large mass of parietal cells in DU patients might be due to the long-term trophic effect of gastrin on parietal cells, and 6-12 months after *H*p eradication, the MAO (representing parietal cell mass) fell significantly; this investigation supports the viewpoint; ② atrophic pangastritis: the degree and extent of gastritis affect destructive number of cells (D, G and parietal) which lead to the released amounts of SS, gastrin and acid in severe destruction; the resultant hyperchlorhydria tends to ulcer formation, and hypochlorhydria to develop carcinoma; pangastritis involving much more D cells and parietal cells may play an important role in imbalance of gastrin-SS equilibrium; ③ increased cytokines (TNF-α and IL-1β)in *H*p infection lead to gastrin-SS imbalance with hyperchlorhydria or hypochlorhydria, and then forming DU or carcinoma; ④ hypergastrinemia of *H*p (CagA) gastritis is due to decreased density of D cells; ⑤ water extract of either *H*p(CagA and VacA) positive or *H*p(CagA and VacA) negative delayed ulcer healing as compared with saline controls in rats, because of impairment of gastrin-SS link; ⑥ in *H*p(+) DU patients, the amount change of T lymphocyte subsets was obviously correlated with those of gastric active inflammation, serum gastrin, and SS in gastric juice, indicating that gastrin and SS played a role in immune regulation. Gastrin-SS equilibrium restores after *H*p

eradication. SS may be the most widely effective gastrointestinal hormone in human body, and it is worthy of further studies[42].

Hp INFECTION AND GASTRIN RELEASING PEPTIDE (GRP)

GRP can stimulate gastric acid secretion, and is particularly valuable in detecting disturbances of gastric secretory function of patients with DU and *H*p infection. Its attractiveness lies in the fact that it simultaneously activates many physiological control processes, both stimulatory and inhibitory. This facilitates the detection of a defect in any of the controls involved in regulating biological function. Other gastrointestinal functions such as gallbladder contraction, pancreatic secretion and gastroesophageal motility are subject to complex regulatory controls, and GRP may also be of value in investigating disturbances of these processes[43].

GRP effect on gastrin and SS mRNAs in humans infected with Hp

GRP stimulates gastrin secretion, but also inhibits its release via SS. Exogenous GRP stimulates a greater increase in plasma gastrin concentrations in *H*p infected patients than in uninfected controls. This is due to less inhibition on gastrin mRNA in *H*p infection, probably because of low stimulated SS levels in *H*p infection[44].

PAO from GRP in DU patients before and after Hp eradication

In a study of gastric acid increment in DU patients, the GRP stimulated PAO (PAOGRP) and pentagastrin stimulated PAO (PAOPG) were measured in *H*p positive DU patients and in *H*p negative as controls. This study has shown that BAO, PAOGRP and PAOPG are significantly higher in *H*p positive DU than in *H*p negative controls. All decreased significantly six months after *H*p eradication to fall within the range of controls. These results are compatible with a hypothesis that acid hypersecretion in DU is caused by *H*p infection[45]. Peterson's investigation showed a similar result that GRP stimulated hypergastrinemia and hyperchlorhydria which were lowered to normal range after *H*p eradication[46].

*H*P INFECTION AND GROWTH FACTORS

Hp infection and epidermal growth factor (EGF)

EGF was found in at least seven individuals, and four of them were expressed in gastrointestinal tract. They were EGF, transforming growth factor alpha (TGF-α), amphiregulin (AR), and heparin binding-epidermal growth factor (HB-EGF). EGF and TGFα have the same receptor, EGFr. EGFs combined to their receptors which widely existed over cellular membrane to regulate cell growth and play biological roles. EGF serves gastrointestinal tract with cell growth, ulcer healing and suppression of acid secretion[47].

Acute exposure to *H*p caused cell damage and impaired the processes of cell migration and proliferation in cultured gastric mucosal cells *in vitro*. EGF-related growth factors play a major role in protecting gastric mucosa against injury, and are involved in the process of gastric mucosal healing. In the study of Romano *et al*, using MKN 28 gastric mucosal cells (derived from gastric adenocarcinoma), *H*p increased mucosal (MKN 28 cells) generation of EGF-related peptides; the inhibitory effect of *H*p on the reparative events mediated by EGF-related growth factors might play a role in the pathogenesis of *H*p-induced gastrointestinal injury[48].

*H*p inhibits both EGF binding to its receptors and EGF-stimulated gastric cell proliferation, and they are the mechanisms of peptic ulcer formation and its difficulty in healing[49-52]. In a study of gastric luminal release of EGF, the stomach was capable of secreting large amounts of EGF, and pentagastrin appeared to be a potent stimulus to gastric EGF release; the *H*p infection reduced the release of gastric EGF, and eradication of *H*p resulted in the augmentation of basal and pentagastrin-induced EGF release into the stomach. Since the eradication of *H*p infection in DU patients resulted in DU healing which was accompanied by an increase in EGF release, conclusively, EGF plays a crucial role in DU healing[53,54]. Accordingly, it also plays a major role in ulcer formation.

Hp infection and hyperproliferation of gastric mucosal epithelium

The overexpression of C-myc gene protein and EGFr (receptor of EGF) may be the molecular basis for hyperproliferation of gastric mucosal epithelium in *H*p infection[55].

Hp infection and growth factors in gastric juice

The EGF concentrations in gastric juice were affected by *H*p and pH. There were four situations in NUD patients studied: ① EGF was 80% lower in *H*p(+) than in *H*p(-); ② those with pH<4.0 in gastric juice had significantly lower EGF concentrations; ③ those with gastric juice pH>4 showed similar conce ntrations of EGF in both *H*p (+) and *H*p(-) groups; ④ those with both *H*p (+) and pH<4.0 had further reduction in EGF concentrations. These results suggested that *H*p may elaborate factors that accelerate its proteolytic degradation or inhibit its rate of synthesis and/or secretion; pH reduction (<4) may increase EGF degradation; the diminished content of EGF at low pH, especially in *H*p-positive patients, may

facilitate the development of mucosal damage. The TGF-α concentrations in gastric juice remained unaffected by *H*p or pH[56].

The cytoprotective effect of sulglycotide

In studying *H*p protease activity and its suppression by sulglycotide, it was found that the *H*p protease evoked a 61.7% degradation of PDGF (platelet derived growth factor) and a 62.3% degradation of TGFβ; introduction of sulglycotide to the reaction assay system caused a dose-dependent inhibition in PDGF and TGFβ proteolysis by the *H*p protease; the maximal inhibitory effect was obtained with sulglycotide at 100mg·L^{-1}, at which dose an 84.4% decrease in PDGF and 88.3% decrease in TGFβ degradation were achieved; the results provide a strong evidence for the effectiveness of sulglicotide in the protection of gastric mucosal growth factors against degradation by *H*p[57].

Eradication of Hp related to EGF and TGF

EGF and TGF-α- are potent gastric secretory inhibitors, mitogens, and mucosal protectors, and their gastric mucosal expression and luminal contents are closely related to *H*p infection. A study of DU and NUD patients showed that chronic *H*p infection and resulting antral gastritis were associated with increased plasma gastrin and increased mucosal cell proliferation, probably due to enhanced expression of EGF and TGF-α; the *H*p eradication decreased plasma gastrin, but the increase in gastric EGF and TGF-α contents was sustained, suggesting that they may be involved in ulcer healing[58].

Effect of *H*p infection on gastric mucosal expression of EGF, TGF-α, and EGFr. In a study of Konturek *et al*, the DU patients with *H*p(+) were accompanied by increased mucosal expression and contents of TGF-α, EGF, and EGFr, and eradication of *H*p infection enhanced all of them and contributed to ulcer healing[59]. Russo *et al* also indicated that *H*p eradication resulted in a significant increase in expression of EGF and TGF-α; *H*p possibly inhibited the mucosal expression of EGF and TGF-α[60]. The results from different authors seem not wholly consistent. It is appropriate to study further.

Implications of Hp, mucosal growth factors and gastric acid in path ogenesis of DU and gastric carcinoma

It has been revealed that patients with DU and gastric carcinoma possessed 3 common features which contributed to the pathogenesis of the two diseases: they were *H*p infection, increase in gastric mucosal and luminal growth factors (EGF, TGF-α), and hypergastrinemia. They remained different in hyperchlorhydria in DU patients, and in patients with gastric carcinoma. These changes returned to normal values two years after *H*p eradication in DU patients. The hypochlorhydria was possibly due to atrophy of oxyntic mucosa and overexpression of growth factors in gastric mucosa may be implicated in the pathogenesis of both DU and gastric cancer. Hypergastrinemia, hypochlorhydria, and increase in mucosal growth factors are predisposing to gastric cancer[61].

Hp infection and insulin-like growth factor-¢ñ (IGF-I)

Taha *et al* measured gastric and fasting serum concentrations of IGF-I in patients with and without *H*p infection. As a result, IGF-I was detected at very low concentrations in gastric juice and in mucosal incubates. The median serum IGF-I concentration was 88μg·L^{-1} in the patients infected with *H*p compared with 90μg·L^{-1} in the non-infected controls; IGF-I concentrations significantly dropped to 77μg·L^{-1} following eradication therapy. Conclusively, the similarity in baseline ICF-I concentrations in the presence and absence of *H*p suggests that their subsequent drop after treatment is more likely to be produced by the treatment[62].

*H*P INFECTION AND OTHER GASTROINTESTINAL HORMONES

Hp infection and insulin

It is true that *H*p gastritis resulted in increased secretion of basal and meal-stimulated gastrin, which is also a physiologic amplifier of insulin release. In order to confirm whether *H*p gastritis may enhance nutrient-stimulated insulin secretion, both glucose and a mixed meal stimulated insulin response were investigated in *H*p positive gastritis and *H*p negative control subjects. The areas under the curve (AUC) for serum insulin following both oral glucose and a mixed meal in the patients with *H*p gastritis were significantly higher than those of non-*H*p controls. After *H*p eradication, the AUC for serum insulin following oral glucose and mixed meal decreased significantly, and serum basal and meal-stimulated gastrin levels also obviously decreased. These results suggest that *H*p gastritis enhances glucose and meal-stimulated insulin release probably by increasing gastrin secretion[63].

Hp infection and glicentin

Glicentin seems to promote intestinal metaplasia (IM) in the gastric mucosa. In order to clarify whether *H*p infection accelerates glicentin gene expression, glicentin mRNA was investigated using gastric biopsies. The results disclosed that glicentin mRNA was significantly correlated with histological IM and was positively correlated with *H*p infection. Conclusion is that *H*p infection is associated with

the induction of glicentin in the gastric mucosa, thus supporting the hypothesis that *H*p infection accelerates IM of the stomach[64].

Hp infection and cholecystokinin (CCK)

In healthy subjects, CCK has the feedback control of postprandial gastrin release and gastric acid secretion , but in *H*p-positive DU patients the CCK loses its control effect. Eradication of *H*p restores the inhibitory effect of CCK on postprandial gastrin release and gastric acid secretion. This suggests that *H*p infection eliminates or lessens the inhibitory effect of CCK on gastrin release[65].

Hp infection and gastric inhibitory polypeptide (GIP)

There was no significant difference of serum GIP levels among groups of gastrectomy (total, subtotal), healthy subjects, *H*p infection, age, gender, body mass index, smoking. Only the elapsed time since operation in patients following total gastrectomy exhibited a significant positive correlation with their GIP levels ($r = 0.89$, $P<0.05$). Hence GIP is less important in mediating gastric acid secretion, and *H*p does not influence its levels[66].

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